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1001 Pennsylvania Avenue, NW, Washington, DC 20004-2595 ▪ p202 624-2500 ▪ f202 628-5116

December 11, 2001

BOX PCT
Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Attorney Docket No 2260/50666

Re: Transmittal Letter to the United States
Designated/Elected Office (DO/EO/US)
Concerning a Filing Under 35 U.S.C. §371

International Application No.: PCT/JP00/04226
International Filing Date: 28 June 2000

Priority date claimed: 29 June 1999
Priority application number: 11-183345

Inventorship: Toshio KASAMA
Mitsuru NOTO
Susumu OGURO
Isao HANAZOME
Rena TATEKAWA

Title: OPHTHALMIC OINTMENT FOR TREATING INFECTIVE EYE DISEASES

Enclosed herewith for entering the national stage in the United States is the above-referenced international application.

APPLICANT WISHES THAT THE ANNEXES TO THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT REPLACE THE APPROPRIATE PAGES OF THE CLAIMS AS FILED.

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. §371.

2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. §371.

3. [ ] This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [ ] A copy of the International Application as filed (35 U.S.C. §371(c)(2))

   a. _____ is transmitted herewith (required only if not transmitted by the International Bureau).

   b. __X__ has been transmitted by the International Bureau

   c. _____ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [X] A translation of the International Application into English (35 U.S.C. §371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))

   a. _____ are transmitted herewith (required only if not transmitted by the International Bureau)

   b. _____ have been transmitted by the International Bureau

   c. _____ have not been made; however, the time limit for making such amendments has NOT expired

   d. __X__ have not been made and will not be made

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)) is:

   [X] Attached in the regular manner.
   [ ] NOT included, but deferred under P.L. 97-247.

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5))

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [X] Two Assignments of the invention in favor of the following organization is enclosed for recordation. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
TOA PHARMACEUTICAL CO., LTD.

13. [X] A FIRST Preliminary Amendment.

[ ] A SECOND or SUBSEQUENT Preliminary Amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [X] Other items of information:

[ ] Form PCT/RO/101 Request (in English/in French)

[ ] Small Entity Declaration Under 37 C.F.R. 1.27

[ ] Copy of Form PCT/DO/EI/905 (Notification of Missing Requirements)

[ ] _____ Sheets of Formal Drawings
[ ] _____ Sheets of Informal Drawings

[ ] The content of the paper and computer readable copy of the attached Sequence Listing, submitted in accordance with 37 CFR §1.821(c) and (e), respectively, are the same.

[X] Kindly appoint as associate attorneys (if not already a principal attorney) or agents:

Herbert I. Cantor, Reg. No. 24,392; James F. McKeown, Reg. No. 25,406; Donald D. Evenson, Reg. No. 26,160; Joseph D. Evans, Reg. No. 26,269; Gary R. Edwards, Reg. No. 31,824; and Jeffrey D. Sanok, Reg. No. 32,169

INTERNATIONAL APPLN. NO.: PCT/JP/04226
ATTORNEY DOCKET NO.: 2260/50666

[X] The total amount due for the filing fee in this case is:

[ ] Based on Small Entity Status

Total Number of Claims: 11
Total Independent Claims: 1

Basic filing fee, $890/$445.	$	890.00
Independent Claims above 3, $84/$42 ea.. . . .	$	
Total claims in excess of 20, $18/$9 ea. . . .	$	
Multiple dependency penalty, $280/$140	$	
Declaration surcharge, $130/65	$	0.00
English translation surcharge, $130	$	
TOTAL FILING FEE DUE	$	890.00

Please forward all communications regarding this application to the undersigned at the letterhead address.

Respectfully submitted,

Herbert I. Cantor
Reg. No. 24,392

HIC/tcv

THE COMMISSIONER IS AUTHORIZED TO CHARGE $890 FOR THE FILING FEE AND $80 ASSIGNMENT RECORDING FEES AND ANY ADDITIONAL FEES WHICH MAY BE REQUIRED OR CREDIT ANY OVERPAYMENT TO DEPOSIT ACCOUNT NO. 05-1323. THIS FORM IS FILED IN DUPLICATE.

THIS IS A GENERAL AUTHORIZATION EXCLUDING ONLY PAYMENT OF THE ISSUE FEE.

Attorney Docket: 2260/50666
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	TOSHIO KASAMA ET AL	
Serial No.:	TO BE ASSIGNED	Group Art Unit:
Filed:	CONCURRENT HEREWITH	Examiner:
Title:	OPHTHALMIC OINTMENTS FOR TREATING INFECTIVE EYE DISEASES	

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to calculation of the filing fee and prior to examination, please amend the above-identified application as follows:

IN THE SPECIFICATION

Page 1, line 1, cancel "Technical Field" and insert --BACKGROUND OF THE INVENTION--

line 7, cancel "Background Art"

Page 2, line 14, cancel "Disclosure of the invention" and substitute therefor --SUMMARY OF THE INVENTION--

Page 4, line 12, cancel "Best Mode for Carrying Out the Invention" and insert --DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS--

Page 11, line 1, cancel "Claims" and insert --WHAT IS CLAIMED IS:--

IN THE CLAIMS

Please amend Claims 2-5 as follows:

--2. (Amended) An ophthalmic ointment as claimed in Claim 1, wherein said eye diseases are caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

3. (Amended) An ophthalmic ointment as claimed in Claim 1, wherein said eye diseases are caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE).

4. (Amended) An ophthalmic ointment as claimed in Claim 2, wherein said infective eye disease is keratitis.

5. (Amended) An ophthalmic ointment as claimed in Claim 3, wherein said infective eye disease is keratitis.--

Please insert the following new claims:

--6. (New) An ophthalmic ointment as claimed in Claim 1, wherein said vancomycin hydrochloride is present in an amount of from 0.1 to 3.0%.

7. (New) An ophthalmic ointment as claimed in Claim 6, wherein said vancomycin hydrochloride is present in an amount of from 0.3 to 1.0%.

8. (New) An ophthalmic ointment as claimed in Claim 1, further comprising a member of the group consisting of liquid paraffin, white petrolatum, purified lanolin, gelation hydrocarbon, polyethylene glycol,

hydrophilic ointment base, white ointment base, Macrogol, ointment base, simple ointment base, and mixtures thereof.

9. (New) An ophthalmic ointment as claimed in Claim 8, further comprising an excipient selected from the group consisting of antiseptics, surfactants, stabilizers, alcohols, esters, oils, and mixtures thereof.

10. (New) An ophthalmic ointment as claimed in Claim 9, said antiseptic is selected from the group consisting of parahydroxybenzoate, chlorobutanol, and benzalkonium chloride, said surfactant is selected from the group consisting of polysorbate 80, polyoxyl 40 stearate, and polyoxyethylene hydrogenated castor oil, said stabilizer is selected from the group consisting of sodium edetate, citric acid, and salts thereof, said alcohol is selected from the group consisting of glycerol, lanolin alcohol, and cetanol, said ester is selected from the group consisting of isopropyl myristate, and ethyl linoleate, and said oil is selected from the group consisting of olive oil and triglycerides of middle-chained fatty acids.

11. (New) A method of treating infective eye diseases comprising topically administering an effective amount of the ophthalmic ointment of Claim 1.--

IN THE ABSTRACT

Please substitute the abstract submitted herewith on a separate page for theoriginal abstract.

REMARKS

It is respectfully requested that the above amendments be entered prior to calculation of the filing fee and prior to examination. The amendments have been made to place the application in better form for U.S. practice and to round out the coverage to which Applicants are entitled. No new matter has been added.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #2260/50666).

Respectfully submitted,

December 11, 2001

Herbert I. Cantor
Registration No. 24,392

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HIC:tcv

APPENDIX

IN THE CLAIMS

Please amend Claims 2-5 as follows:

--2. (Amended) An ophthalmic ointment [for treating infective eye diseases] as claimed in Claim 1, wherein said eye diseases are caused by methicillin-resistant *Staphylococcus aureus* (MRSA)[, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.]

3. (Amended) An ophthalmic ointment [for treating infective eye diseases] as claimed in Claim 1, wherein said eye diseases are caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE)[, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride].

4. (Amended) An ophthalmic ointment as claimed in Claim 2, wherein said infective eye disease is [for treating] keratitis [caused by MRSA, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride].

5. (Amended) An ophthalmic ointment as claimed in Claim 3, wherein said infective eye disease is [for preventing] keratitis [caused by MRSE, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride].--

ABSTRACT OF THE DISCLOSURE

Ophthalmic ointments for treating infective eye diseases which are particularly effective against infective eye diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE) and contain as the active ingredient from 0.01 to 5.0% of vancomycin hydrochloride. Compared with intravenous administration, topical administration of these ophthalmic ointments is accompanied with no problem of the occurrence of side effects such as renal toxicity and thus enables the maintenance of a therapeutically effective concentration.

SPECIFICATION

OPHTHALMIC OINTMENT FOR TREATING INFECTIVE EYE DISEASES

Technical Field

The present invention relates to ophthalmic ointments for treating infective eye diseases, and more particularly, to ophthalmic ointments for treating infective eye diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE).

Background Art

Development of antibiotics has been recognized to be a battle against relentlessly emerging resistant strains. In recent years, methicillin-resistant *Staphylococcus aureus* (MRSA) has been attracted significant attention as a new type of multiple drug-resistant bacteria which are responsible for infections in various medical fields. Also, there is growing concern about nosocomial MRSA infection as the number of reported cases of MRSA infection increases every year.

Gram-positive cocci, in particular staphylococci, are by far the most prevalent pathogens of infective eye diseases such as neonatal dacryocystitis, chronic dacryocystitis, conjunctivitis, hordeolum externum, blepharoadenoma, keratitis, corneal ulcer, blepharitis (including blepharitis marginalis), endophthalmitis, orbital cellulitis, Stevens-Johnson syndrome, orbital infections, and postoperative infections (including infections of buckling). Recently, it has been reported that the cases of eye infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSA) are on the increase.

Furthermore, as an intraocular implant to the patients

suffering from cataract become a popular procedure, postoperative MRSA or MRSE infections have become a matter of considerable concern.

Despite the growing concern over MRSA infection in the field of ophthalmology, no effective ophthalmic ointment has been proposed thus far as a therapeutic formulation of eye infections, especially those caused by MRSA.

Accordingly, it is an objective of the present invention to provide an ophthalmic ointment for treating infective eye diseases, and in particular, to provide an ophthalmic ointment for treating infective eye diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE).

Disclosure of the Invention

In view of the above-mentioned objective, one aspect of the present invention provides an ophthalmic ointment for treating infective eye diseases containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

Among others, the present invention is particularly directed to an ophthalmic ointment for treating infective eye diseases caused by MRSA or MRSE. More particularly, the present invention provides an ophthalmic ointment for treating infective eye diseases caused by methicillin-resistant *S. aureus* (MRSA) or methicillin-resistant *S. epidermidis* (MRSE) containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

As used herein, the term "infective eye diseases" refers to infective diseases including neonatal dacryocystitis, chronic dacryocystitis, conjunctivitis, hordeolum externum, blepharoadenoma, keratitis, corneal ulcer, blepharitis (including blepharitis marginalis), endophthalmitis, orbital cellulitis,

Stevens-Johnson syndrome, orbital infections, and postoperative infections (including infections of buckling). Among others, the present invention is particularly directed to an ophthalmic ointment for treating or preventing of keratitis caused by MRSA (which may be referred to simply as "MRSA keratitis", hereinafter).

Thus, in a more specific embodiment, the present invention provides an ophthalmic ointment for treating MRSA keratitis containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride. In this regard, the present invention also provides an ophthalmic ointment for preventing MRSA keratitis containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

In the first place, the present inventors paid their attention to vancomycin hydrochloride, which is used as the agent of the first choice to treat MRSA infections, in an effort to provide the ophthalmic ointment for treating infective eye diseases in accordance with the present invention. No medical ointment containing vancomycin hydrochloride had been proposed until then and no one had ever conceived of the idea of using vancomycin hydrochloride in ophthalmic ointments.

At that point, the present inventors prepared an ophthalmic ointment containing vancomycin hydrochloride, as the agent of the first choice used to treat MRSA infections, applied the ointment to treat infective eye diseases, especially keratitis caused by MRSA, and discovered that the ointment exhibited excellent efficacy as a therapeutic formulation for treating such infective eye diseases.

Thus, the present invention is of absolute novelty in that it provides an ophthalmic ointment containing vancomycin hydrochloride, which no one has ever conceived of using in this

form.

Vancomycin hydrochloride is little absorbed in the living body when orally administered and is hardly distributed to eyes tissue when intravenously injected. Therefore, maintaining the effective concentration of vancomycin in eye tissue requires a large quantity of solution for bolus intravenous injection, which may cause renal toxicity.

Accordingly, the ophthalmic ointment of the present invention, which is topically available of vancomycin hydrochloride, eliminates the above-mentioned disadvantages and provides a highly effective therapeutic formulation for treating infective eye diseases.

Best Mode for Carrying Out the Invention

In an ophthalmic ointment of the present invention containing vancomycin hydrochloride as an active ingredient, the content (*i.e.*, concentration) of vancomycin hydrochloride is from 0.01 to 5.0%, preferably from 0.1 to 3.0%, more preferably from 0.3 to 1.0%, based on the amount of ophthalmic ointment preparation.

In the course of the study, the present inventors applied the ophthalmic ointment containing vancomycin hydrochloride at a concentration of 0.3% or 1.0%, to corneas of rabbits suffering MRSA keratitis and discovered that the ointment was effective not only in preventing keratitis caused by MRSA keratitis but also in curing the disease.

A preferred ointment base used to prepare the ophthalmic ointment of the present invention may be one that has been used in conventional ophthalmic ointments. In particular, the preferred base may be liquid paraffin, white petrolatum, purified lanolin, gelation hydrocarbon, polyethylene glycol, hydrophilic ointment base, white ointment base, absorptive ointment base,

Macrogol (Trade Name) ointment base, simple ointment base, and the like.

The ophthalmic ointment of the present invention may contain further conventional excipients other than the ointment base in the range of without affecting the intended functions and stability of vancomycin hydrochloride to be contained. Examples of such excipients include antiseptics such as parahydroxybenzoate, chlorobutanol, benzalkonium chloride and the like; surfactants such as polysorbate 80, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil and the like; stabilizers such as sodium edetate, citric acid, and salts thereof; alcohols such as glycerol, lanolin alcohol, cetanol and the like; esters such as isopropyl myristate, ethyl linoleate and the like; and oils such as olive oil and triglycerides of middle-chained fatty acids.

The ophthalmic ointment of the present invention can be produced as follows: if necessary, antiseptics, surfactants, stabilizers, alcohols, esters or oils are blended with an ointment base such as liquid paraffin or white petrolatum placed in a mortar or a mixing machine for ointment to form a mixture. This is followed by addition of vancomycin hydrochloride, and the resulting mixture is mixed until uniform and kneaded to form the ophthalmic ointment. The ointment thus prepared is filled into a bottle or tube for ointment to obtain the ophthalmic ointment containing vancomycin hydrochloride of the present invention.

The ophthalmic ointment containing vancomycin hydrochloride of the present invention obtained in the above-described manner is efficacious against infective eye diseases including neonatal dacryocystitis, chronic dacryocystitis, conjunctivitis, hordeolum externum, blepharoadenoma, keratitis, corneal ulcer, blepharitis (including blepharitis marginalis), endophthalmitis, orbital

cellulitis, Stevens-Johnson syndrome, orbital infection, and postoperative infections (including infections of buckling).

The ophthalmic ointment of the present invention for treating infective eye diseases is particularly effective against those infective eye diseases caused by MRSA or MRSE. Among others, the ophthalmic ointment of the present invention is particularly effective for treating or preventing of keratitis caused by MRSA.

Examples

The present invention will now be described in detail with reference to specific examples, but it is to be noted that the present invention is not limited by these Examples in any way.

Example 1

20g of liquid paraffin and 79g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 1g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous ophthalmic ointment containing 1% of vancomycin hydrochloride.

Example 2

15g of liquid paraffin and 84g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 1g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous ophthalmic ointment containing 1% of vancomycin hydrochloride.

Example 3

20g of liquid paraffin and 79.7g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 0.3g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous

ophthalmic ointment containing 0.3% of vancomycin hydrochloride.

Example 4

15g of liquid paraffin and 84.9g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 0.1g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous ophthalmic ointment containing 0.1% of vancomycin hydrochloride.

Example 5

20g of liquid paraffin and 79.97g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 0.03g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous ophthalmic ointment containing 0.03% of vancomycin hydrochloride.

Example 6

15g of liquid paraffin and 82g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 3g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous ophthalmic ointment containing 3% of vancomycin hydrochloride.

Example 7

15g of liquid paraffin and 80g of white petrolatum were placed in a mortar and were mixed and kneaded until uniform. This was followed by addition of 5g of vancomycin hydrochloride and the resulting mixture was thoroughly kneaded to form a homogenous ophthalmic ointment containing 5% of vancomycin hydrochloride.

Example 8: Storage Stability Test

The storage stability of ophthalmic ointments containing

vancomycin hydrochloride obtained in Examples mentioned above was tested.

Each of the ophthalmic ointments was filled in a plastic tube and was stored in a thermostatic bath kept at 25°C or at 30°C. As a stability test, the remaining ratio of vancomycin hydrochloride was measured with the passage of time by high-performance liquid chromatography. In the 2 months stability tests at 25°C or at 30°C, the ophthalmic ointments of the present invention each showed excellent stability.

The results are shown in Table 1 below.

Table 1

Concentration of agents	Initial	Remaining Ratio of Vancomycin / HCl			
		25°C/ 1 month	25°C/ 2 months	30°C/ 1 month	30°C/ 2 months
0.1%	100%	98.3%	97.7%	97.0%	96.4%
0.3%	100%	98.5%	97.1%	97.4%	96.0%
1.0%	100%	98.7%	97.1%	97.7%	96.3%

As can be seen from the results above, the ophthalmic ointments of the present invention each showed excellent stability.

Example 9: Pharmacological Test

1. Methods

A group of four white rabbits, weighing about 2.5kg, was used for each test. A solution of MRSA for inoculation was prepared by taking the bacteria of MRSA cultured on blood agar with a loop and suspending them in saline (1 loop/1ml). In accordance with a method described by Kondo *et al* (*Jpn. Rev. Clin. Opthalmol.*, 75(1981): 1421), the bacteria were inoculated onto each cornea in 17 spots by injecting the MRSA suspension using a tuberculin syringe having 27G needle. Subsequently, 0.1ml of the

bacterial suspension were applied to both eyes. The ointment containing vancomycin hydrochloride of the present invention was then applied to the right eyes whereas only the base of the ointment was applied to the left eyes. The ointment and the base were applied 5 times a day for 2 days. The corneas were observed 48 hours after the inoculation.

Four concentrations of vancomycin hydrochloride, namely 0.03%, 0.1%, 0.3% and 1%, were used.

2. Results

In the eyes (left) applied only the base, the formation of abscess-like circular infiltration and strong iritis with fibrin at each needling positions were observed and significant eye mucus suffering from keratitis caused by MRSA was also observed.

In contrast, keratitis was completely prevented in the eyes to which the ointment containing 1.0% or 0.3% of vancomycin hydrochloride was applied (*i.e.*, right eyes).

Further, punctate infiltration was observed only in one or two of the inoculation spots in each of the eyes to which the ointment containing 0.1% of vancomycin hydrochloride (*i.e.*, right eyes) was applied whereas many punctate infiltration as well as partially orbicular infiltration were observed in the eyes to which the ointment with 0.03% of vancomycin hydrochloride (*i.e.*, right eyes) was applied.

In view of the results above, it can be concluded that the ophthalmic ointment of the present invention containing 0.3% or more of vancomycin hydrochloride is capable of completely preventing MRSA keratitis and the ointment may be effective against MRSA keratitis even when the amount of vancomycin hydrochloride is less than 0.3%.

It should be noted that an ophthalmic ointment tends to remain in a conjunctival sac for a prolonged period of time while releasing drug in a sustained manner and the ophthalmic ointment

of the present invention is considerably more effective as compared to when vancomycin is applied through dropping since it is designed to maintain the concentration of vancomycin in eye tissue higher than the minimum inhibitory concentration (MIC) for a prolonged time.

Industrial Applicability

As has been described thus far, the present invention provides an ophthalmic ointment that is effective against MRSA infective eye diseases in the field of ophthalmology. Considering the fact that no effective therapeutic formulation has ever been proposed in this field, the possible impact of the present invention will be of considerable medical importance.

In particular, intravenous administration of vancomycin requires a large quantity of solution for bolus intravenous injection in order to maintain the effective concentration of vancomycin since vancomycin is hardly distributed to eye tissue. This may lead to various side effects including renal toxicity.

In contrast, the ophthalmic ointment of the present invention is provided in the form of a topical ophthalmic ointment, which no one has ever conceived of, and therefore is capable of avoiding the side effects while maintaining the effective concentration of vancomycin in eye tissue. Accordingly, the ophthalmic ointment of the present invention can be used as a highly effective therapeutic formulation in treating infective eye diseases.

Claims

1. An ophthalmic ointment for treating infective eye diseases, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

2. An ophthalmic ointment for treating infective eye diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA), containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

3. An ophthalmic ointment for treating infective eye diseases caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE), containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

4. An ophthalmic ointment for treating keratitis caused by MRSA, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

5. An ophthalmic ointment for preventing keratitis caused by MRSE, containing as an active ingredient from 0.01 to 5.0% of vancomycin hydrochloride.

UTILITY PATENT
OR DESIGN
SOLE OR JOINT

CROWELL & MORING, LLP
UNITED STATES LETTERS PATENT
DECLARATION AND POWER OF ATTORNEY

ATTORNEY'S DOCKET NO.

As a below named inventor, I declare that I believe I am the original, first and sole inventor if only one name is listed at Item 201 below, or a joint inventor if plural names are listed below at Items 201 et. seq. of subject matter which is claimed and for which a patent is sought for the invention entitled:

which is described and claimed in:

101 [ ] the attached specification [x] the specification in application Serial No. PCT/JP00/04226 filed 28/06/00
(for declaration not accompanying application papers)

and *(if applicable)* amended on

102 [ ] international (PCT) application No. filed and as amended on (if any)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose all information known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim the benefit of priority, under Title 35, United States Code, §119, of any foreign application(s) for patent or inventor's certificate listed in Item 103 below and have also identified in Item 103 below any foreign application(s) for patent or inventor's certificate having a filing date before that of the application for which priority is claimed.
I hereby claim the benefit, under Title 35, United States Code, §120, of any U.S. application(s) listed in Item 105 below. If this application is a continuation-in-part, insofar as the subject matter of any of the claims thereof is not disclosed in the prior U.S. application(s) identified in Item 105 below in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior U.S. application(s) identified in Item 105 below and the national or PCT international filing date of this application.

FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 (6 if a Design) MONTHS PRIOR TO THE FILING DATE OF THIS APPLICATION THE PRIORITY OF WHICH WHERE PERMITTED IS HEREBY CLAIMED UNDER 35 U.S.C. §119

	COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED YES	NO
103	Japan	JP 11-183345	29/06/99	X	

105	THIS APPLICATION IS A: [ ] CONTINUATION [ ] DIVISION [ ] CONTINUATION-IN-PART OF PRIOR U.S. APPLICATION	SERIAL NO.	FILED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

(6)

JAMES F. MCKEOWN
Registration No. 25,406

HERBERT I. CANTOR
Registration No. 24,392

DONALD D. EVENSON
Registration No. 26,160

JOSEPH D. EVANS
Registration No. 26,269

GARY R. EDWARDS
Registration No. 31,824

JEFFREY D. SANOK
Registration No. 32,169

SEND CORRESPONDENCE TO:	CROWELL & MORING, L.L.P. P.O. Box 14300 Washington, D.C. 20044-4300	DIRECT TELEPHONE CALLS TO: 202-628-8800

Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR	LAST NAME: KASAMA	FIRST NAME: Toshio	MIDDLE NAME:
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION: Toshima-ku	STATE OR COUNTRY: Tokyo JPX	CITIZENSHIP: Japanese
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 35-11,Mejiro 4-chome,Toshima-ku,Tokyo 171-0031		
202	FULL NAME OF INVENTOR	LAST NAME: NOTO	FIRST NAME: Mitsuru	MIDDLE NAME:
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION: Kurobe-shi	STATE OR COUNTRY: Toyama JPX	CITIZENSHIP: Japanese
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 223-1,Ikuji,Kurobe-shi,Toyama 939-0066		
203	FULL NAME OF INVENTOR	LAST NAME: OGURO	FIRST NAME: Susumu	MIDDLE NAME:
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	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 885,Dougenji,Tateyama-cho,Nakaniikawa-gun,Toyama 930-0241		

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	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 148,Shimoiino,Toyama-shi,Toyama 931-8443		
205	FULL NAME OF INVENTOR	LAST NAME: TATEKAWA	FIRST NAME: Rena	MIDDLE NAME:
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	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 8-13,Sogawa 3-chome,Toyama-shi,Toyama 930-0083		
206	FULL NAME OF INVENTOR	LAST NAME:	FIRST NAME:	MIDDLE NAME:
	RESIDENCE CITIZENSHIP	CITY OR OTHER LOCATION:	STATE OR COUNTRY:	CITIZENSHIP:
	POST OFFICE ADDRESS	POST OFFICE ADDRESS:		

[ ] Seventh (and more) coinventors on page 3

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issue thereon.

SIGNATURE OF INVENTOR 201: Toshi Kasama	SIGNATURE OF INVENTOR 202: M. noto	SIGNATURE OF INVENTOR 203: S. Oguro
DATE: November 5,2001	DATE: November 7,2001	DATE: November 7,2001
SIGNATURE OF INVENTOR 204: I. Hanazome	SIGNATURE OF INVENTOR 205: R. Tatekawa	SIGNATURE OF INVENTOR 206:
DATE: November 7,2001	DATE: November 7,2001	DATE: